Critical Review Form
Therapy

Out of hospital treatment of acute pulmonary embolism in patients with a low NT-proBNP level, *J Thromb Haemostasis* 2010; 8: 1235-1241

Objective: **To investigate "the safety of outpatient treatment of renodynamically stable patients with PE with a low NT-pro BNP level at presentation." (p. 1236)**

Methods: **Multicenter prospective study at 5 hospitals in the Netherlands between September 2006 and March 2009 in patients age > 18 years with newly diagnosed PE (CT, pulmonary angiogram, high probability V/Q scan, or indeterminate V/Q with LE DVT on Doppler). Outpatient management ensued for those without exclusion criteria and with NT-pro BNP <500 pg/mL. Exclusion criteria included vital sign instability (systolic BP < 90, pulse >100, requiring supplemental oxygen to maintain saturation > 90%), other illness-related reason for admission, pain requiring analgesia, need for acute PE thrombolysis, active bleeding or known hemorrhagic diathesis, pregnancy, in-hospital patients, likelihood of poor compliance, no support system at home, or renal insufficiency.**

All eligible patients were treated with LMWH as bridge to oral anticoagulation therapy (agents not specified but INR monitored, so presumably Coumadin). INR monitoring was performed by the Dutch network of regional anticoagulation services. Cancer patients were treated with LMWH alone (no Coumadin). All patients received information brochure, 24 hour number and, and telephone follow up on Days 2 and 4.

The main outcome was 10-day PE related mortality as per judgment of an independent steering committee. The committee classified fatal outcomes as a) related to PE, b) bleeding, c) cancer, or d) other cause. Secondary outcomes included 10-day readmission rates related to PE or anticoagulation therapy. Investigators also assessed patient satisfaction [PSQ-18] and anxiety at Day 0 vs. Day 10 [HADS-A]. Investigator also evaluated rates of recurrent VTE and major bleeding at 90 days. Major bleeding was defined as ≥ 2 gm/dL drop in Hg requiring transfusion of ≥ 2 units PRBC or bleeding in critical area/organ or contributing to death.

***A priori*, the investigators selected a threshold of 1% PE-related mortality as a stopping point in this study. They planned to enroll 150 consecutive patients. One death at 10-days would represent a 0.67% (95% CI 0-1.9%) mortality rate and the**

study would be stopped. If no deaths at 150 patients the authors planned to continue to 300 patients. With 300 patients one PE-related death would fall below the 1% threshold (0.3%, 95% CI 0-0.98%).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	No, this is an observational trial so no randomization or control group.
2.	Was randomization concealed (blinded)?	No randomization, no blinding.
3.	Were patients analyzed in the groups to which they were randomized?	No randomization so this is a per protocol analysis.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Patients with NT-pro BNP >500 were older (61.2 vs. 53.4 years, p=0.002) with lower baseline oxygen saturation 94.8% vs. 97.1%, (p <0.001) and more likely to have a CHF history. "No differences were found in gender, blood pressure, pulse rate, rate of active malignancy, chronic pulmonary disease or previous VTE between patients with a high NT-pro BNP level and the 152 patients with an NT-pro BNP <500 pg/mL." (p. 1239)
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes, no blinding.
2.	Were clinicians aware of group allocation?	Yes, no blinding.
3.	Were outcome assessors aware of group allocation?	Yes, no blinding.
4.	Was follow-up complete?	Yes. "None of the 152 patients were lost to follow-up during the first 3 months." (p. 1237)

II.	What are the results (answer the questions posed below)?	
1.	How large was the treatment effect?	• 351 PE patients but 68 were excluded (other illness requiring hospitalization = 21, collapse = 10, oxygen <90% = 9, sBP < 90 = 6, psychiatric co-morbidity = 5, asystole = 4, severe hemoptysis = 1, pregnancy = 1, age <18 = 1, no support at home = 10. An additional 9% (25/283) refused to participate in the study and 80/232 patients (34.5%) had NT-pro BNP > 500 leaving **43.3% of PE patients (152/353) eligible and in the study**. • Mean age of the eligible patients with NT-pro BNP <500 was 53.4 ± 14 years (range 20-84) and 51.3% were female and 69.1% discharged directly from ED. **Outcomes** • No deaths the first 10 days (0%) • Seven rehospitalizations in the first 10 days, but only 3 deemed PE-related (2 anxiety, 1 chest pain). Of note, no PE progression on two chest CT's. • No VTE recurrence or major bleed or death at either 10 or 90 days. • 67.8% response rate to patient satisfaction survey with mean out-of-hospital satisfaction score 3.80 (SD 0.97) [0=not satisfied, 5 = very satisfied] • 67.1% returned anxiety score survey on both Day 0 and Day 10 with no significant difference in scores noted [4.29 on Day 0 vs. 4.31 on Day 10, p=0.968] • Amongst the 80 patients with NT-pro BNP >500, one patient had thrombolysis on Day 0 and another

		had thrombectomy secondary to cardiovascular collapse on Day 2. A third patient died on Day 32 of cardiac decompensation.
2.	How precise was the estimate of the treatment effect?	See standard deviations above.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Uncertain. The authors reported no socioeconomic status, insurance status, transportation access to PCP or Thrombo Clinic, or health literacy. Although physiologic response to acute PE probably does not differ across borders and healthcare systems, access to care and patient compliance certainly does based upon governmental support (or lack thereof) for universal healthcare.
2.	Were all clinically important outcomes considered?	No, PE morbidity and mortality, bleeding complications, and patient satisfaction/comfort were reported and are the most important. <u>However, it would be interesting to view physician perspectives and perceived obstacles.</u> Would also like to see how NT-pro BNP adds to PESI score for risk stratification.
3.	Are the likely treatment benefits worth the potential harm and costs?	No formal cost-benefit analysis, but home-based care without hospital expenses is undoubtedly cheaper. If equally safe and effective, as well as acceptable to appropriate patients and clinicians, outpatient PE management might be one area for healthcare systems to choose wisely in reducing costs.
4.	How will you communicate the findings of this study with your patients to facilitate shared decision-making?	One effective method: "Dutch study of low overall quality indicates that home management of PE with LMWH and oral anticoagulation is

		effective in low-risk patients defined by a readily available blood test."

Limitations

1) **Uncertain external validity to urban U.S. healthcare setting with uncertain access to follow up care, heterogeneous insurance status, and widely variable health literacy, not to mention a persistent medical malpractice quagmire.**

2) **Failure to compare NT-pro BNP to PESI (or other PE risk stratification instruments).**

3) **BNP is used at our hospital, not NT-pro BNP. Fortunately, multiple studies have demonstrated that NT-pro BNP correlates with BNP (Sugimoto 2010, Park 2010, Ewald 2008)**

4) **Failure to reference or use STROBE criteria for observational trial.**

5) **Non-randomized so uncertain whether outcomes reflect atypically healthy population (or other unmeasured confounder) showing observed results.**

6) **Failure to measure health literacy, socio-economic status, insurance status, or access to PCP/Thrombo clinic (confounding prognostic variables), all of which could influence likelihood of successful outpatient PE management.**

7) **Failure to assess physician comfort with outpatient PE management (Futterman 2004, Calder 2005, Kabrhel 2010).**

Bottom Line

Post-ED outpatient management of PE with LMWH and Coumadin in the Netherlands appears safe and effective n reliable hemodynamically stable adults with adequate social support and NT-pro BNP <500. Future investigators should assess the added benefit of NT-pro BNP to cheaper/readily available PE risk stratification instruments like PESI.